CLAIMS

What is claimed:

1. A monoclonal antibody that specifically binds to an oligomeric form of human STOP-1.

2. A monoclonal antibody that specifically binds to amino acids 33-52 or 33-53 of human STOP-1.

3. A monoclonal antibody that specifically binds to amino acids 94-243 of human STOP-1.

4. The monoclonal antibody according to claim 3, wherein the monoclonal antibody binds to an oligomeric form of human STOP-1

5. A monoclonal antibody comprising:

(a) a first amino acid sequence comprising:

T - I - X1 - X2- X3-X4

wherein X1 is S, N or T;
wherein X2 is G, N, S or A;
wherein X3 is Y, S or T; and
wherein X4 is D or W.

(b) a second amino acid sequence comprising:

X1-X2-I-X3-P-X4-X5-G-X6-T-X7 (SEQ ID NO:115)

wherein X1 is G or A;

wherein

(1) X2 is an amino acid selected from the group consisting of S, T, A, and X3 is an amino acid selected from the group consisting of R, W and Y; or

(2) X3 is an amino acid selected from the group consisting of S, T, A, and X2 is an amino acid selected from the group consisting of R, W and Y;

wherein X4 is Y or F;

wherein X5 is G, S, T or A;

wherein X6 is N, Y or A;

wherein X7 is N, Y or D; and

(c) a third amino acid sequence comprising the sequence:

C-X1-X2-X3-G-G-X4-X5-X6-X7-X8-X9-X10-X11 (SEQ ID NO:116)

wherein X1 is A, S or T;

wherein X2 is basic amino acid;

wherein X3 is any amino acid;

wherein X4 is a hydrophobic amino acid;

wherein any one of X5- X8 can be any amino acid or can be missing, and at least one of X5-X8 is an aromatic amino acid or a hydrophobic amino acid;

wherein X9 is an aromatic or hydrophobic amino acid;

wherein X10 is D or A; and

wherein X11 is Y or V.

3. The antibody according to claim 5, wherein the first amino acid sequence is selected from any one of the group consisting of TISGSD, TITNSD and TISGSW.

4. The antibody according to claim 5, wherein the second amino acid sequence is selected from any one of the group consisting of GRISPYGGNTN, ATIYPYGGYTY and AWIAPYSGATD

5. The antibody according to claim 5, wherein the third amino acid sequence is selected from any one of the group consisting of CARVGGLKLLFDY, CARGGGMDGYVMDY and CAREGGLYWVFDY.

6. The antibody according to claim 5, where in the antibody comprises:

(a) the first amino acid sequence TISGSD;

(b) the second amino acid sequence GRISPYGGNTN; and

(c) the third amino acid sequence CARVGGLKLLFDY; or a variant of said antibody.

7. The antibody according to claim 5, where in the antibody comprises:

(a) the first amino acid sequence TITNSD;

(b) the second amino acid sequence ATIYPYGGYTY; and

(c) the third amino acid sequence CARGGGMDGYVMDY; or a variant of said antibody.

8. The antibody according to claim 5, where in the antibody comprises:

(a) the first amino acid sequence TISGSW;

(b) the second amino acid sequence AWIAPYSGATD; and

(c) the third amino acid sequence CAREGGLYWVFDY; or a variant of said antibody.

9. A monoclonal antibody comprising (a) a first amino acid sequence TISNYG; (b) a second amino acid sequence GRISPSNGSTY; and (c) a third amino acid sequence CAKCSVRFAY, or a variant of said antibody.

10. A monoclonal antibody comprising (a) a first amino acid sequence TINNYD; (b) a second amino acid sequence GYISPPSGATY; and (c) a third amino acid sequence CARMVGMRRGVMDY or a variant of said antibody.

11. The monoclonal antibody according to any one of claims 5 to 10, wherein the first amino acid sequence is within residues 28-33 of a heavy chain according to the Kabat numbering system, the second amino acid sequence is within residues 49-58 of a heavy chain according to the Kabat numbering system and the third amino acid sequence is within residues 92-102 according to the Kabat numbering system.

12. A monoclonal antibody comprising the amino acid sequence of:

(a) the heavy chain sequence of FIG.27;

(b) the heavy chain sequence of FIG.28;

(c) the heavy chain sequence of FIG.29;

(d) the heavy chain sequence of FIG.30;

(e) the heavy chain sequence of FIG.31; or

(f) the heavy chain sequence of FIG.34; or a variant thereof.

13. The monoclonal antibody according to claim 12, further comprising the amino acid sequence of :

(a) the light chain sequence of FIG.27; or

(b) the light chain sequence of FIG.34; or a variant thereof.

14. A monoclonal antibody having the biological characteristics of an antibody selected from the group consisting of S7 encoded by the nucleic acid molecule deposited on March 25, 2003 as designation V0350-4-S7, S4 encoded by the nucleic acid molecule deposited on March 25, 2003 as designation V0350-2b-S4, S9 encoded by the nucleic acid molecule deposited on March 25, 2003 as designation V0350-2b-S9, S16 encoded by the nucleic acid molecule deposited on March 25, 2003 as designation V0350-4-S16, F5 encoded by the nucleic acid molecule deposited on March 25, 2003 as designation V0350-5 and 6B12 produced by the hybridoma cell line deposited on March 28, 2003 as designation 6B12.1.7 in the American Type Culture Collection (ATCC) , 10801 University Blvd., Manassas, VA 20110-2209, USA.

15. A monoclonal antibody that specifically binds to STOP-1, wherein the binding of the antibody to STOP-1 can be inhibited by a second monoclonal antibody selected from the group consisting of S7 encoded by the nucleic acid molecule deposited with ATCC as

designation V0350-4-S7, S4 encoded by the nucleic acid molecule deposited with ATCC as designation V0350-2b-S4, S9 encoded by the nucleic acid molecule deposited with ATCC as designation V0350-2b-S9, S16 encoded by the nucleic acid molecule deposited with ATCC as designation V0350-4-S16, F5 encoded by the nucleic acid molecule deposited with ATCC as designation V0350-5 and 6B12 produced by the hybridoma cell line deposited with the ATCC as designation 6B12.1.7.

16. A monoclonal antibody that specifically binds to STOP-1, wherein the antibody comprises the light and heavy chain sequences of an antibody selected from the group consisting of S7 encoded by the nucleic acid molecule deposited with ATCC as designation V0350-4-S7, S4 encoded by the nucleic acid molecule deposited with ATCC as designation V0350-2b-S4, S9 encoded by the nucleic acid molecule deposited with ATCC as designation V0350-2b-S9, S16 encoded by the nucleic acid molecule deposited with ATCC as designation V0350-4-S16, F5 encoded by the nucleic acid molecule deposited with ATCC as designation V0350-5 and 6B12 produced by the hybridoma cell line deposited with the ATCC as designation 6B12.1.7, and variants thereof.

17. The antibody according to any one of claims 1-16, wherein the antibody is a chimeric or humanized antibody.

18. The antibody according to any one of claims 1-16, wherein the antibody is an antibody fragment or a bispecific antibody.

19. The antibody according to claim 17 or 18, wherein the antibody is conjugated to an agent selected from the group consisting of a growth inhibitory agent, a cytotoxic agent, a detection agent, an agent that improves the bioavailability and an agent that improves the half-life of the antibody.

20. The antibody according to claim 19, wherein said cytotoxic agent is selected from the group consisting of a toxin, an antibiotic and a radioactive isotope.

21. The antibody according to any one of claims 1-16, wherein said antibody is produced in bacteria.

22. The antibody according to any one of claims 1-16, wherein said antibody is produced in CHO cells.

23. A STOP-1 polypeptide variant comprising a STOP-1 polypeptide that cannot be secreted from a cell.

24. The polypeptide variant according to claim 23, wherein the polypeptide is mutated at residue 186.

25. A STOP-1 polypeptide variant comprising a STOP-1 polypeptide that cannot disulfide bind with another STOP-1.

26. The polypeptide variant according to claim 24, wherein the polypeptide is mutated at residue 55.

27. A nucleic acid molecule encoding the antibody according to any one of claims 1-18 or the polypeptide according to any one of claims 23-26.

28. A vector comprising the nucleic acid molecule according to claim 27.

29. A host cell comprising the nucleic acid molecule according to claim 27.

30. A composition comprising a STOP-1 antagonist and a pharmaceutically acceptable carrier, wherein the antagonist specifically binds STOP-1 and said binding can be inhibited by the monoclonal antibody, 6B12.

31. The composition according to claim 30, wherein the antagoinist specficaly binds to a residues within the residues 33-52 of human STOP-1

33. A composition comprising an antagonist of a STOP-1 polypeptide and a stromal targeting agent.

34. A composition comprising the monoclonal antibody according to any one of claims 1 to 18.

35. A composition comprising the polypeptide according to any one of claims 23 to 26.

36. The composition according to claim 34 or 35, further comprising a stromal targeting agent.

37. The composition according to claim 34, wherein the stromal targeting agent is covalently linked to the antagonist.

38. The composition according to claim 34, wherein the stromal targeting agent is covalently linked to the monoclonal antibody.

39. The composition according to claim 35, wherein the stromal targeting agent is covalently linked to the polypeptide.

40. The composition according to any one of claims 33-36, wherein the stromal targeting agent recognizes a stromal cell of a tumor.

41. A composition comprising the nucleic acid molecule according to claim 27.

42. A method for producing a STOP-1 polypeptide or an anti-STOP-1 antibody comprising the step of culturing a cell comprising a nucleic acid molecule according claim 27.

43. The method according to claim 42, wherein the cell is a bacterial cell or a mammalian cell.

44. A method for producing a STOP-1 polypeptide comprising the step of culturing a mammalian cell that comprises a nucleic acid molecule encoding the STOP-1 polypeptide and that is deficient in proteoglycan synthesis.

45. The method according to claim 41, wherein the cell line that is deficient in proteoglycan synthesis is deficient in galactosyltransferase I activity.

46. The method according to claim 45, wherein the cell line is a CHO-psbg cell line.

47. A method for diagnosing or monitoring a tumor of a patient comprising the step of comparing the amount of STOP-1 protein in a normal tissue to the amount of STOP-1 protein in a tissue being tested from the patient.

48. The method according to claim 47, wherein the amount of STOP-1 in the normal tissue and tumor tissue is being evaluated based on expression in stromal cells.

49. A method for diagnosing or monitoring a tumor of a patient comprising the step of comparing the amount of STOP-1 protein in a normal tissue to the amount of STOP-1 protein in a tissue being tested from the patient using the monoclonal antibody according to any one of claims 1 to 18.

50. The method according to claim 49, wherein the amount of STOP-1 in the normal tissue and tumor tissue is being evaluated based on expression in stromal cells.

51. A method of preventing or inhibiting the growth of a tumor that overexpresses STOP-1 comprising administering to a patient an antagonist of STOP-1 in an amount effective to inhibit growth of the tumor in the patient.

52. A method of inhibiting the growth of a tumor that overexpresses STOP-1 comprising administering to a patient a composition according to any one of claims 30 to 38 in an amount effective to inhibit growth of the tumor in the patient.

53. The method according to claim 52, wherein the tumor has stromal compartments.

54. The method according to claim 52, wherein the tumor is selected from the group consisting of desmoid tumor, sarcomas, adenocarcinomas, hepatocellular carcinoma, round cell tumors, breast cancer, colon cancer, lung cancer, ovarian cancer, a melanoma, endometrial cancer, glioma, pancreatic cancer and vascular cancer.

55. A method of inhibiting the growth of a cell that overexpresses STOP-1 comprising the step of inhibiting the secretion of STOP-1 from the cell.

56. The method according to claim 55, wherein the secretion is inhibited by overexpressing in the cell a STOP-1 protein that cannot be secreted from the cell.

57. The method according to claim 56, wherein the STOP-1 protein that cannot be secreted is mutated at residue 186.

58. A method for preventing disulfide binding between STOP-1 molecules comprising a step selected from the group consisting of:

(1) mutating STOP-1-encoding DNA molecules at residue cysteine 55;

(2) expressing STOP-1 proteins that are mutated at residue cysteine 55 in the presence of naturally-occuring STOP-1 proteins; and

(3) incubating STOP-1 proteins that are mutated at residue cysteine 55 with naturally-occuring STOP-1 proteins.

59. A method for cleaving STOP-1 comprising the step of incubating STOP-1 with a protease selected from the group consisting of a matrix metalloprotease-7 (MMP-7) and a matrix metalloprotease-9 (MMP-9).

60. The method according to claim 59, further comprising the step of monitoring the STOP-1 cleavage products produced.

61. A method for determining the presence of a STOP-1 polypeptide in a sample comprising exposing a sample suspected of containing the STOP-1 polypeptide to an anti-STOP-1 antibody and determining binding of said antibody to a component of said sample.

62. An article of manufacture comprising:

(a) a composition of matter comprising a modified STOP-1 polypeptide, a STOP-1 polypeptide variant or a STOP-1 antagonist;

(b) a container containing said composition; and

(c) a label affixed to said container, or a package insert included in said container referring to the use of said polypeptide variant, modified polypeptide or antagonist in the treatment of a proliferative disorder.

63. The method according to claim 51, wherein the STOP-1 antagonist has any activity selected from the group consisting of (1) binds to residues within human STOP-1 that the 6B12 antibody binds; (2) binds to a residue within at least residues 33-52 or 33-53 of human STOP-1; and (3) can be competed from binding to STOP-1 by the 6B12 antibody.

64. A method of inducing cell migration in vitro comprising administering to a cancer cell or an endothelial cell a STOP-1 polypeptide in an amount effective to induce migration of said cell.

65. A method of testing the activity of a candidate antagonist or agonist of STOP-1 comprising the steps of exposing a first endothelial or cancer cell to STOP-1, exposing a second endothelial or cancer cell to STOP-1 and the candidate antagonist or agonist, and comparing the migration of the first and second endothelial or cancer cells.

66. The method according to claim 64 or 65, wherein the cell is a HUVEC cell.

67. A method of treating a disease or condition associated with excessive, inappropriate or uncontrolled angiogenesis in a mammalian subject, comprising administering to the subject a STOP-1 antagonist thereof in an amount effective to treat the disease, wherein the STOP-1 antagonist has any activity selected from the group consisting of (1) binds to residues within human STOP-1 that the 6B12 antibody binds; (2) binds to a residue within at least residues 33-52 of human STOP-1; and (3) can be competed from binding to STOP-1 by the 6B12 antibody.

68. A composition comprising a pharmaceutically acceptable carrier and an immunoadhesin that comprises a STOP-1 polypeptide and an Fc portion of an antibody.

69. The composition according to claim 68, wherein the composition comprises an oligomeric form of STOP-1 that comprises greater than three STOP-1 polypeptides.

70. A composition comprising a pharmaceutically acceptable carrier and a molecule that potentiates the binding of a STOP-1 polypeptide to a cell surface.

71. The composition according to claim 70, wherein the molecule aggregates STOP-1 on a cell surface.

72. The composition according to claim 70, wherein the potentiating molecule is an anti-STOP-1 antibody.

73. An article of manufacture comprising:

(a) a composition of matter comprising a molecule that potentiates STOP-1 binding to cells or the composition according to claims 68-72;

(b) a container containing said composition; and

(c) a label affixed to said container, or a package insert included in said container referring to the use of said molecule or agonist in the treatment or amelioration of an illness that would benefit from increased angiogenesis.

74. A method of inducing angiogenesis in a patient who would benefit from increased angiogeneis by administering a therapeutically effective amount of a STOP-1 potentiator or the composition according to any one of claims 68-72.

75. The method according to claim 74, wherein the agonist is an anti-STOP-1 antibody.

76. A method for identifying or evaluating a candidate STOP-1 antagonist comprising the steps of exposing STOP-1 to a cancer cell in the presence of the candidate STOP-1 antagonist, exposing STOP-1 to a cancer cell in the absence of the candidate STOP-1 antagonist and comparing the binding of STOP-1 to the cancer cell in the presence and the absence of the candidate STOP-1 antagonist.

77. A method for evaluating a STOP-1 antagonist comprising the steps of exposing STOP-1 to a cancer cell in the presence of the STOP-1 antagonist and measuring or observing the binding of STOP-1 to the cancer cell.

78. The method according to claim 76 or claim 77, wherein the cancer cell is a breast cancer cell.

79. A method for identifying or evaluating a candidate STOP-1 antagonist comprising the steps of exposing STOP-1 to an endothelial cell in the presence of a candidate STOP-1 antagonist, exposing STOP-1 to an endothelial cell in the absence of a candidate STOP-1 antagonist and comparing the binding of STOP-1 to the endothelial cell in the presence and the absence of the candidate STOP-1 antagonist.

80. A method for evaluating a STOP-1 antagonist comprising the steps of exposing STOP-1 to an endothelial cell in the presence of the STOP-1 antagonist and measuring or observing the binding of STOP-1 to the cancer cell.

81. A method for evaluating a STOP-1 potentiator comprising the steps of exposing STOP-1 to an endothelial cell in the presence of the STOP-1 potentiator and measuring or observing the binding of STOP-1 to the cancer cell.

82. A method for evaluating a STOP-1 agonist comprising the steps of exposing STOP-1 to an endothelial cell in the presence of the STOP-1 agonist and measuring or observing the binding of STOP-1 to the cancer cell.